139. (Amended) A method of using ex-vivo hyaluronan perfusion to mobilize hematopoietic and [dentritic-type] dendritic-type cells out of an ex-vivo organ that has already been harvested from the donor [by the infusion of] comprising infusing an effective amount of hyaluronan to a patient wherein the form of hyaluronan is selected from hyaluronan and pharmaceutically acceptable salts thereof having a molecular weight less than 750,000 daltons.

141. (Amended) A method using hyaluronan infusion to mobilize hematopoietic cells and dendritic-type cells away from/out of an organ graft that shows signs of immunologic rejection [by the infusion of] comprising infusing an effective amount of hyaluronan to a patient wherein the form of hyaluronan is selected from hyaluronan and pharmaceutically acceptable salts thereof having a molecular weight less than 750,000 daltons.

REMARKS

The Present Invention

The present invention pertains to methods for cell mobilization using *in vivo* treatment with hyaluronan (HA).

The Pending Claims

Claims 94 and 101-170 are pending currently. All of the pending claims are directed to methods for cell mobilization using hyaluronan. Reconsideration of the pending claims is respectfully requested.

Summary of the Office Action

Applicant acknowledges, with appreciation, the Office Action's indication that the restriction requirement, as it pertains to Groups VII and X, i.e., claims 125-126 and 133-136, has been withdrawn. In addition, the Office Action requests that the Applicant provide copies of the references that were cited in the Information Disclosure Statement

(IDS). The Office Action also requests that Applicant clarify the priority information pursuant to 35 U.S.C. § 371. In addition, the Office Action indicates that, if claim 111 is found to be allowable, claim 131 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof.

Moreover, the Office has rejected claims 103, 106-111, 114-126, 130, 131, 133-136, 138, 139, 141, 143, and 144 pursuant to 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Finally, claims 103, 106-111, 114-126, 130-136, 138, 139, 141, 143, and 144 stand rejected under 35 U.S.C. § 103(a) as obvious over either of Hamman et al. (i.e., *The Journal of Immunology*, 154, 4073-4080) or Han et al. (i.e., *Journal of Cellular Physiology*, 168, 97-104, 1996), in view of Falk et al. (i.e., U.S. Patent 5,827,834).

Amendments to the Specification

Applicant has adopted the Examiner's suggestion to amend the specification to recite the claim of priority. Thus, no new matter has been added by way of this amendment.

Discussion of Amendments to the Claims

The claims have been amended, with respect to form, so as to more particularly point out and distinctly claim the subject matter of the invention. In particular, claims 103 and 116 have been amended to eliminate the phrase "the stimulation." Claim 103 also has been amended to recite the feature that the form of hyaluronic acid is administered to a "patient." This amendment is supported by the specification at, for example, page 23, line 36 – page 24, line 19, wherein the specification discloses the ability of HA to mobilize populations of hematopoietic and dendritic cells in humans and other mammals. This amendment also finds support in the specification at, for example, page 9, lines 13-16, wherein the specification states that the term patient is interchangeable with the terms human and mammal. In addition, claim 103 has been amended to clarify that the present method provides a means for stimulating the production of cells in the bone marrow and for stimulating the release of cells from the

bone marrow and other tissue sites into the blood (see, e.g., page 19, lines 16-37, of the present specification).

Meanwhile, claim 111 has been amended with respect to form to eliminate the phrase "the administration" and claims 124 and 125 have been amended merely to clarify certain phrasing. Furthermore, claim 126 has been amended to delete "the" from the phrase "the peripheral blood." Also, claim 131 has been re-written into independent form such that it is directed to a method of modulating symptoms of allergy or asthma. Claims 139 and 141 have been amended to more positively recite the steps of the claimed methods (see, e.g., page 29, lines 1-29, and lines 30-37, respectively).

No new matter has been added by way of any of these amendments. A complete recitation of the pending claims, after entry of the present amendments, is attached hereto for the convenience of the Office.

Information Disclosure Statement

Pursuant to the Office Action's request, applicant submits herewith copies of the references provided with the previously-submitted Information Disclosure Statement dated September 10, 1998. Applicant requests that the Examiner kindly acknowledge consideration of these references in the Examiner's next communication.

Priority Information

Applicant has adopted the Examiner's suggestion and amended the specification to insert the priority information.

Discussion of Claim 131

The Office Action provisionally objects to claim 131 as being duplicative of claim 111, pursuant to 37 C.F.R. § 1.75. Although applicant disagrees with the objection, in order to expedite prosecution, applicant has amended claim 131 herein, and the objection to claim 131 is moot in view of this amendment. In particular, claim 131 has been amended so that it now is in independent form such that it is directed to a method of

modulating symptoms of allergy or asthma. Accordingly, applicant requests withdrawal of this provisional objection.

Discussion of the Indefiniteness Rejections

The Office has rejected claims 103, 106-111, 114-126, 130, 131, 133-136, 138, 139, 141, 143, and 144 as being indefinite under 35 U.S.C. § 112, second paragraph. These rejections are in part moot in view of the revisions to the claims made herein, and are traversed in part.

Specifically, the Office contends that claims 103 and 116 lack antecedent basis for the term "the stimulation." Because claims 103 and 116 have been amended to eliminate the phrase "the stimulation," applicant respectfully requests withdrawal of this objection. The Office contends that claim 103 is indefinite also because the phrase "enhancing the stimulation of cells production/release" does not particularly point out that which Applicant intends to claim. This objection is moot in view of the revised preamble for claim 103, which refers to a method for stimulating the production of cells in the bone marrow and/or the release of cells from the bone marrow and other tissue sites into the blood. Moreover, the Office contends that claim 103 is indefinite because it fails to recite to whom or to what the hyaluronic acid is to be administered. This objection, likewise, is moot inasmuch as claim 103, as revised herein, recites the feature that hyaluronic acid is administered to a "patient."

The Office also contends that the phrase "effective amount" renders claims 103, 111, 139, and 141 indefinite. Applicant respectfully requests reconsideration of this rejection. According to MPEP § 2173.05(c), the proper test to determine whether the phrase "an effective amount" is indefinite or not is "whether or not one skilled in the art could determine specific values for the amount based on the disclosure." *See* MPEP § 2173.05(c) (citing *In re Mattison*, 509 F.2d, 563, 184 USPQ 484 (CCPA 1975)). Moreover, the trend is "to accept a limitation such as 'an effective amount' as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim." *See* MPEP § 2173.05(c) (citing *Ex parte Skuballa*, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989)).

Specifically, courts have held that the phrase "an effective amount" is definite when the amount is not critical and those skilled in the art would be able to determine from the written disclosure, including the examples, what constitutes an effective amount. *See* MPEP § 2173.05(c) (citing *In re Halleck*, 422 F.2d 911, 164 USPQ 647 (CCPA 1970)).

In view of the foregoing, applicant respectfully submits that the phrase "effective amount" is definite in view of the written disclosure. The specification at page 14, line 3 – page 18, line 7, for example, provides examples of particular amounts of hyaluronic acid and/or pharmaceutically acceptable salts that may be administered to patients. Moreover, the specification provides guidance in determining an effective amount at, for example, page 23, lines 16-25. In view of these disclosures in the specification, and in view of the fact that the Office has failed to point to any prior art that gives rise to uncertainty about the scope of claims 103, 111, 139, and 141, the applicant respectfully submits that the phrase "an effective amount" does not render these claims indefinite.

In addition, the Office contends that claim 111 lacks positive antecedent basis for the term "the administration." In view of the amendment to claim 111 to eliminate this phrase, this rejection is moot and should be withdrawn. The Office also contends that claim 111, by its preamble, is drawn to a method for the administration of hyaluronic acid. The Office then contends that claim 112 is indefinite because it fails to recite the steps involved in such a method. Claims 111 and 112 are independent claims. As such, the definiteness of claim 112 does not depend upon claim 111. Contrary to the assertion in the Office Action, claim 112 does in fact recite a method step. Therefore, applicant respectfully requests reconsideration of the indefiniteness rejection of claim 112. If applicant has not properly understood the Office's concern regarding claim 112 such that the rejection has not properly been addressed, the Examiner is invited to call the undersigned attorney to expedite the prosecution of the present application.

Also, with respect to claim 111, the Office contends that what the applicant intends to claim is unclear in view of the recitation of "enhancing, stimulating and releasing . . . cells . . . into the blood." Applicant traverses this rejection. It is noteworthy that MPEP § 2173.02 requires only that the claims define the patent subject matter "with a reasonable degree of particularity and distinctness." Moreover, MPEP §

2173.02 specifies that claim language must be analyzed in view of the applicant's disclosure, the prior art, and the "claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

In these respects, applicant respectfully submits that the phrase "enhancing, stimulating and releasing . . .cells . . . into the blood" in claim 111 would be clear to the ordinarily skilled artisan in view of the applicant's disclosure at, for example, page 11, lines 16-31, wherein the specification discloses the role of hyaluronic acid in initiating hematopoietic cell mobilization from the bone marrow to the blood. Accordingly, what is intended to be claimed in claim 111 is clear and definite, and, as such, applicant requests that this objection be withdrawn.

Furthermore, the Office contends that the term "predetermined intervals" in claim 116 has no particular art-recognized meaning, and has not been adequately defined in the specification. Applicant respectfully requests reconsideration of this contention. By reading the disclosure at, for example, page 10, line 19, wherein an example is provided of a patient receiving doses, one of ordinary skill in the art would understand what the term "predetermined intervals" means. Moreover, the specification at page 23, line 22, provides an example of a predetermined interval (e.g., weekly).

The Office also contends that, although the phrase "treating a patient for," seems to require a disorder as the object of "for" in claims 124 and 125, the applicant recites "mobilizing hematopoietic cell," a desirable phenomenon. In order to expedite prosecution, applicant has amended claims 124 and 125 to implement the Office Action's suggestion that the claims recite --treating a patient in order to mobilize hematopoietic cells--. Accordingly, the amendments to claims 124 and 125 obviate the basis for the Office's objection .

The Office contends that claim 126 lacks antecedent basis for "the peripheral blood." Claim 126 has been amended to delete "the" from the phrase. Accordingly, the rejection of claim 126 is moot. In addition, the Office contends that claim 136 lacks antecedent basis for "the form of hyaluron." Applicant traverses this rejection. In this respect, claim 136 depends upon claim 133, which in turn depends upon claims 124-128,

which provide the requisite antecedent basis. Accordingly, this objection should be withdrawn.

Finally, the Office contends that claims 139 and 141 are indefinite because they lack any steps of the claimed methods. Claims 139 and 141 have been amended to more positively recite the steps of the methods. As such, the rejection of claims 139 and 141 should be withdrawn.

Since all of the pending claims satisfy the requirements of 35 U.S.C. § 112, the rejections thereunder should be withdrawn.

Discussion of the Obviousness Rejection

The Office contends that claims 103, 106-111, 114-126, 130-136, 138, 139, 141, 143, and 144 are unpatentable under 35 U.S.C. § 103(a) in view of the combination of either Hamann et al. or Han et al. in view of Falk et al. Specifically, the Office contends that Hamann et al. teaches that hyaluronic acid stimulates growth of megakaryocyte progenitors and that hyaluronic acid has implications for the treatment of asthma. The Office also contends that Han et al. teaches that hyaluronic acid stimulates growth of CD34+ selected umbilical cord blood cells into differentiated eosinophils, and that hyaluronic acid may be useful for the treatment of throbocytopenias. Moreover, the Office contends that Falk et al. teaches the administration of multiple doses at time intervals and the therapeutic potential of hyaluronic acid in patients. By combining these references, the Office Action contends that it would have been *prima facie* obvious to one of ordinary skill in the art to modify the method disclosed by Hamann et al. or Han et al. to stimulate the production or release of hematopoietic or dendritic cells. Applicants respectfully traverse the § 103(a) rejection.

To establish a *prima facie* obviousness rejection under § 103(a), the references, when combined, (1) must disclose or reasonably suggest all elements of the claimed invention, (2) must establish evidence of some teaching or suggestion to make the suggested combination, and (3) must establish a reasonable expectation of success arising from the proffered combination. *See* MPEP § 706.02(j). The Office has failed to make these requisite showings.

First, the Office has failed to show that the references, when combined, disclose or suggest all of the elements of the claimed invention. All of the rejected claims are premised upon the use of hyaluronic acid to stimulate the *in vivo* production and/or release of cells such as hematopoietic and dendritic cells into the blood. Despite the contentions of the Office, Hamann et al. and Falk et al., or Han et al. and Falk et al., when combined, do not disclose or suggest the *in vivo* production/release of cells from the bone marrow into the blood. Hamann et al. merely discloses an *in vitro* system wherein undifferentiated progenitor cells proliferate. Similarly, Han et al. merely discloses the *in vitro* proliferation of megakaryocyte progenitors.

Moreover, although Falk et al. discloses *in vivo* methods of using hyaluronic acid, these methods do not include the *in vivo* production/release of cells from the bone marrow into the blood. Rather, they pertain, for example, to transporting a non-steroidal anti-inflammatory drug (NSAID) and hyaluronic acid to a site in a patient, decreasing side effects that may accompany the administration of an NSAID and hyaluronic acid, and treating anorectal disease using hyaluronic acid. Clearly, methods such as these do not relate to, or suggest, the *in vivo* use of hyaluronic acid to produce and release cells from the bone marrow and tissue into the blood. Accordingly, Hamann et al., Han et al., and Falk et al. (alone or in combination) do not suggest, let alone disclose, all of the elements of the claimed invention.

Even assuming *arguendo* that either Hamann et al. or Han et al. in view of Falk et al. discloses or suggests the elements of the claimed invention, a prima facie showing of obviousness also requires some reason or suggestion to make the combination, i.e., some motivation to combine. According to MPEP § 2143.01, the prior art must suggest the desirability of the combination, and the Office must provide objective evidence of a motivation to combine (MPEP § 2143.01). The Office has failed to provide such objective evidence. Rather, the Office simply renders a conclusory statement that it "would have been obvious for a person of ordinary skill in the art at the time of the invention to administer hyaluronic acid to a patient in order to stimulate the production or release of hematopoietic or dendritic cells, including stem cells or red blood cells." The Office has failed to render objective evidence of why an ordinarily skilled artisan would

be inclined to combine references pertaining to the *in vitro* development of progenitor cells with a reference pertaining to methods such as transporting a non-steroidal anti-inflammatory drug (NSAID) and hyaluronic acid to a site in a patient, decreasing side effects that may accompany the administration of an NSAID and hyaluronic acid, and treating anorectal disease using hyaluronic acid, particularly to achieve the claimed methods. Accordingly, the Office has failed to meet the second requirement for a *prima facie* case of obviousness.

Finally, to complete a *prima facie* showing of obviousness, the Office must establish that an ordinarily skilled artisan, after combining the references, would have a reasonable expectation of success to realize the claimed method. *In re O'Farrell*, 853 F.2d 894, 904, 7 USPQ2d at 1681. The Office, however, has also failed to meet this burden. According to the Office, Hamann et al. teaches a method of using hyaluronic acid that stimulates the growth of megakaryocyte progenitors. Similarly, the Office points out that Han et al. teaches that hyaluronic acid stimulates the growth of CD34+ selected umbilical cord blood cells into mature, differentiated eosinophils, and indicates that such activity may be useful for the management of throbocytopenias. Yet, the Office fails to acknowledge the unpredictability of biological systems, and summarily dismisses the fact that the Hamann et al. and Han et al. references do not enable any *in vivo* methods for the differentiation of progenitor cells.

The applicant respectfully submits that because the *in vitro* activity of a compound is not necessarily predictive of its activity *in vivo* or its effectiveness as a therapeutic or prophylactic agent because of the complexity of biological systems, it is not reasonable to expect that a compound *in vitro* will behave in the same manner as a compound *in vivo*. For example, a compound may behave differently when in the controlled conditions of a buffered solution or a cell-derived solution than when located within the complex environment inside and outside a cell, tissue, or organ in a mammal. Moreover, just because a compound gives positive results *in vitro*, it does not necessarily follow that there is a reasonable probability of success for therapeutic use of the compound *in vivo*. *In re Carroll*, 601 F.2d 1184, 1186, 202 USPQ 571, 572-73 (CCPA 1979). Although the Office proffers precatory statements regarding the potential

therapeutic and clinical benefits that may arise from the Hamann et al. and Han et al. studies and that purportedly render the present invention obvious, these precatory comments are insufficient to establish a prima facie case of obviousness. *See* In re Gangadharam, *No. 89-1435, 1989 WL 127023, at **1, **2 (Fed. Cir. 1989).* Therefore, it is impossible to suggest that an ordinarily skilled artisan at the time of the present invention would have known that the Hamann et al. and Han et al. *in vitro* studies could have the *in vivo* effects that the present invention claims.

Since none of the cited references discloses or fairly suggests the present invention as recited in the pending claim, the present invention is patentable over the cited references. Accordingly, the obviousness rejections should be withdrawn and the application allowed.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: November 9, 2000

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In re Application of: Pilarski
U.S. Application No. 09/142,557

CERTIFICATE OF MAILING

I hereby certify that this AMENDMENT (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: November 9, 2000 J. Mihitiouk